REMARKS

Applicants have carefully studied the Office Action mailed January 13, 2011, which issued in connection with the above-identified patent application. The present response is intended to be fully responsive to all points raised by the Examiner and is believed to place the claims in condition for allowance. Favorable consideration and allowance of the present claims are respectfully requested.

I. Telephone Interview with Examiner Boesen

Applicants gratefully acknowledge the courtesy shown by Examiner Agnieszka Boesen during the telephonic interview with Applicants' representative, Irina Vainberg, on February 15, 2011. The Interview Summary mailed by the USPTO on February 22, 2011 is believed to accurately reflect the substance of the interview.

II. Pending Claims and Status of Prosecution

Claims 1, 3, 4, 9-13, 15-20, 22, 23, 28-31, 33-37, 40, 45, 46, 51-53 and 56 were pending in this application. Claims 11-13, 15-19, 29-31, 33-37, and 40 have been withdrawn from consideration as directed to non-elected invention. Claims 1, 3, 4, 9, 10, 20, 22, 23, 28, 45, 46, 51-53, and 56 are under examination.

Applicants respectfully note that the present Non-Final Office Action is the **7th** Office Action in the present prosecution (the first Office Action being mailed December 28, 2007). Out of the seven Office Actions, only two Office Actions were Final Office Actions. The last three Office Actions have been Non-Final Office Actions. Of these, the Office Action dated May 11, 2010 was vacated by the Examiner after an interview with the applicants and replaced by another Non-Final Office Action dated July 23, 2010. No claim amendments were made in response to the Non-Final Office Action dated July 23, 2010. Furthermore, ALL rejections presented in the Non-Final Office Action dated July 23, 2010 have been withdrawn in light of applicants' arguments, as specified at

pages 2-3 of the present Office Action. Now, the Examiner has issued yet another Non-Final Office Action.

The present Office Action is the result of a new search conducted by the Examiner, which was not prompted by any action taken by applicants, as no claims were amended in response to the last Office Action. As explained in detail below, the newly cited reference, Krasemann et al., which has been uncovered in the new search does not constitute the "best available prior art", since not only does it not disclose immunization with prion PROTEIN (and, in fact, discloses immunization with DNA expression vectors) but it is far less relevant than prior art already applied by the Examiner to reject claims in this application.

It is respectfully submitted that the present Office Action should not have been issued as it is not in conformity with the USPTO's Principles of Compact Prosecution.

In accordance with USPTO's Principles of Compact Prosecution (see, e.g., http://www.uspto.gov/patents/law/exam/compact_prosecution.pdf), US Patent Examiners are to conduct an initial search which is as complete as possible and need only update the prior search in most instances and not "re-search" the application. Further, prior art rejections should ordinarily be confined strictly to the best available art and only reasonable rejections should be made (MPEP 706.02). The present Office Action is inconsistent with the USPTO's Principles of Compact Prosecution. This is the 7th Office Action for this application. All of the rejections from the previous Office Action have been withdrawn. The newly cited prior art is less relevant than the art previously cited and overcome. This application is clearly patentable over the cited prior art for the reasons set forth below. The present Office Action needlessly prolongs prosecution of this application. This application is believed to be in condition for passage to allowance and such action is respectfully requested.

III. Obviousness Rejections

Claim 1 has been rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann et al. (Journal of Immunological Methods, 1996, Vol. 199, p. 109-118) (hereafter "Krasemann") in view of Sigurdsson et al. (American Journal of Immunology, 2002, Vol. 161, p. 13-17) (hereafter, "Sigurdsson").

Claim 20 and its dependent claims 28, 51, and 52 have been rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann in view of Sigurdsson as applied to claim 1 and further in view of U.S. Patent 5,733,760 by Lu et al. ("Lu"), Chabalgoity et al. (Vaccine, 2001, Vol. 19, p. 460-469, in IDS of 11/18/2005) ("Chabalgoity"), and Grones and Turna (Biochemical and Biophysical Research Communications, 1995, Vol. 206, pp. 942-947) ("Grones").

Claims 3, 4, 22, 23, 45-46, and 53, which depend from claim 1 or claim 20, have been rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann in view of Sigurdsson as applied to claims 1 and 20 in view of Lu and Chabalgoity, and further in view of U.S. Patent Publication No. 2002/0194634 by Dunne et al. ("Dunne") and Benkirane et al. (Journal of Biological Chemistry, 1993, Vol. 268, p. 26279-26285, in IDS of 11/18/2005) ("Benkirane").

Claims 9, 10, and 56, which depend from claim 1, have been rejected under 35 U.S.C. § 103(a) as being obvious over Krasemann in view of Sigurdsson as applied to claim 1 in view of Lu and Chabalgoity, and further in view of Clements et al. (U.S. Patent No. 6,440,423) ("Clements"), and Kleanthous et al. (U.S. Patent No. 6,585,975) ("Kleanthous").

The rejections are respectfully traversed.

The only new reference cited by the Examiner is Krasemann. All other references have been cited in the obviousness rejections presented in the Non-Final Office Action dated July 23, 2010 and have been overcome in light of applicants' arguments, as specified at pages 2-3 of the present Office Action.

The present claims recite compositions comprising a non-infectious, non-pathogenic mammalian prion **protein** selected from the group consisting of mouse, bovine, deer, elk, and sheep prion protein, which compositions are suitable for mucosal administration and, when introduced to a mammal's mucosal immune system, elicit a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response.

The Examiner asserts that Krasemann teaches a composition comprising recombinant non-infectious, nonpathogenic human prion **protein** resuspended in PBS and mucosal immunization of mice with this composition. The Examiner further states that, while Krasemann does not teach non-infectious mouse, bovine, deer, elk or sheep prion protein, it would have been prima facie obvious to provide a composition suitable for mucosal administration comprising Sigurdsson mouse non-infectious prion protein and Krasemann's PBS, because Sigurdsson teaches a composition comprising an isolated non-infections mouse prion protein and CFA adjuvant.

Applicants respectfully note that, in contrast to the Examiner's assertion, Krasemann does NOT teach a composition comprising recombinant non-infectious, nonpathogenic human prion **protein**, but only teaches compositions comprising **DNA** expression vectors encoding prion proteins. The whole point of the Krasemann article is that DNA immunization (as opposed to protein immunization) should be used in order to induce an effective immune response. This is emphasized in the Title and Abstract of the article. Krasemann actively *teaches away* from the protein-based immunogenic compositions of the present invention and, in fact, provides a clear evidence of non-obviousness of the present invention.

Applicants note the following statements in the Discussion section at pages 115 and 116 of Krasemann (emphasis added):

> To generate antibodies against prion proteins, classical **antigen** immunization techniques have generally been unsuccessful. The few existing sera and monoclonal antibodies are neither species-specific nor do they differentiate between normal and

> disease-associated isoforms (Barry et al., 1988; Gabizon et al., 1988; Kascsak et al., 1987; Serban et al., 1990). **Immune tolerance of laboratory animals seems to be the problem.** All animals carry their species-specific prion gene and may have either deleted their immune competent cells or rendered them anergic during maturation of their immune system. Since the interspecies homology between prion proteins is high, **even proteins from distantly related species do not break tolerance and induce an immune response**...
>
> In contrast, to raise prion protein-specific immune sera directed against different human prion proteins, **we have immunized $Prp^{o/o}$ mice by injecting DNA expression vectors encoding the cellular and several disease associated human prion proteins**...
>
> **In our hands. an efficient immune response depends on the site of DNA inoculation, the pre-treatment of the muscle tissue prior to injection and the use of the immediate early promoter of the human cytomegalovirus**...
>
> The **genetic immunization against pathogens has important safety related advantages over protein and adjuvant procedures, especially for the prion protein** since it is still unclear whether the protein itself might be able to start an infection...
>
> There are additional reasons which might render the **DNA-mediated immunization superior to conventional vaccinations**...

As acknowledged by the Examiner, Sigurdsson discloses compositions containing prion **protein**. Combining Krasemann and Sigurdsson is thus improper, since Krasemann directly teaches away from immunization using **protein** compositions such as those disclosed in Sigurdsson. It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). See also MPEP 2145.

As discussed in detail in response to the previous Office Action, Sigurdsson's CFA- and IFA-containing compositions did not induce an immune response that was sufficient to treat prionoses. As further discussed in detail in response to the previous Office Action, the secondary references (cited again in the present Office Action) do not cure the deficiency of Sigurdsson, because none of them teach or suggest that Sigurdsson's CFA- and IFA-containing compositions could be administered mucosally without CFA or IFA to successfully induce a Th2-mediated mucosal immune response, since Sigurdsson's compositions were hardly effective with CFA and

IFA. As evidenced by the above citations from Krasemann, the understanding in the field at the time of the present invention was that it is extremely difficult to break tolerance to antigens regarded by the immune system as self antigens, such as e.g., endogenous prion proteins. Therefore, the skilled artisan would have had no reason to expect that Sigurdsson's composition would work better if administered mucosally with a different adjuvant such as PBS.

The Examiner has already acknowledged the persuasiveness of applicants' arguments with respect to Sigurdsson and all secondary references by her removal of prior obviousness rejections. Since Krasemann does not teach **protein**-containing immunogenic compositions and teaches away from the other references cited by the Examiner, the present obviousness rejections are believed to be overcome and withdrawal of these rejections is respectfully requested.

IV. Claim Limitation "Suitable for Mucosal Administration"

In the Office Action, the Examiner insists that the limitation of independent claims 1 and 20, "suitable for mucosal administration," is not considered limiting, because it recites an intended use. Applicants respectfully disagree with this claim construction and note that the Examiner's position is inconsistent with her own position in the Office Action dated October 26, 2009, where she gave patentable weight to this limitation and re-instated prior art rejection over Bachmann et al. (U.S. Patent Publication No. 2003/0219459) when this limitation was removed.

"Suitable for mucosal administration" is a property of the claimed composition. A further property of the claimed composition is that "when introduced to a mammal's mucosal immune system," it "elicit[s] a primarily Th-2-type immune response against an endogenous prion protein of said mammal that is associated with a mucosal IgA humoral immune response and any concomitant immunoglobulin counterpart in other bodily fluids, and is not associated with a primarily Th-1-type cytotoxic T-lymphocyte response." The present claims encompass only those non-infectious, non-pathogenic prion protein-containing compositions which can be administered mucosally and, after they are administered mucosally, induce a Th-2-type immune response (i.e., overcome mucosal tolerance) against an endogenous prion protein (PrP) (self protein).

The understanding in the field at the time of the present invention was that it is extremely difficult to create vaccine compositions which would overcome mucosal tolerance to antigens regarded by the immune system as self antigens, such as e.g., endogenous prion proteins. See the above citations from Krasemann. See also Czerkinsky et al. (Immunological Reviews, 1999, 170:197-222; attached as Exhibit A) stating that "[i]mmunologic unresponsiveness (tolerance) is a key feature of the mucosal immune system, and deliberate vaccination or natural immunization by a mucosal route can effectively induce immune suppression."

As disclosed in detail in the present specification, "suitable for mucosal administration" compositions recited in the present claims comprise delivery vehicles and carriers which allow to effectively overcome mucosal tolerance against an endogenous prion protein upon mucosal administration. See, e.g., paragraphs [0049-0071], [0077-0079], and Examples 1-4 of the application as published (U.S. Patent Publication No. 2007/0059807).

The term "suitable for mucosal administration" as it applies to immunogenic compositions has a very clear meaning in the art. For example, as emphasized in 2005 review by Holmgren and Czerkinsky (Nature Medicine Supplement, 2005, 11(4):S45-S53; attached as Exhibit B),

> The development of mucosal vaccines, whether for prevention of infectious diseases or for oral-tolerance immunotherapy, requires efficient antigen delivery and adjuvant systems. Ideally, such systems should (i) protect the vaccine from physical elimination and enzymatic digestion, (ii) target mucosal inductive sites including membrane, or M, cells, and (iii) at least for vaccines against infections, appropriately stimulate the innate immune system to generate effective adaptive immunity... (p. S50, left col.)
>
> Although effective oral-mucosal vaccines for human use are available, it is increasingly appreciated that the development of a broader range of mucosal vaccines, whether for prevention of infectious diseases or for immunotherapy of autoimmune, allergic or infectious inflammatory disorders, will require access to antigen delivery systems that can help present the relevant 'protective antigens' efficiently to the mucosal immune system as well as effective adjuvants to promote and direct the mucosal immune response toward the desired effect. (p. S51, left col.)

CONCLUSION

In view of the above arguments, it is respectfully submitted that the present claims are now in condition for allowance and such action is earnestly solicited. If the Examiner believes that a telephone conversation would help advance the prosecution in this case, the Examiner is respectfully requested to call the undersigned attorney at (212) 641-2364. The Commissioner is hereby authorized to charge all requisite fees to our Deposit Account No. 06-1050.

Respectfully submitted,

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